SYNTHESIS OF 3-SUBSTITUTED ISOCOUMARINS THROUGH ACYLOXYPALLADATION OF *o*-ALKENYLBENZOIC ACIDS

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Cyclization of *o*-alkenylbenzoic acids in the presence of Pd catalyst and benzoquinone led to 3-substituted isocoumarins in high yield. The isocoumarins obtained were converted to isoquinolones by treatment with primary amines.

KEYWORDS isocoumarin; acyloxypalladation; *o*-alkenylbenzoic acid; palladium(II); benzoquinone; isoquinolone

A wide variety of isocoumarins occur naturally, and the isocoumarin ring system also plays an important role as an intermediate for a synthesis of several natural products.¹⁾ Recently, several biologically interesting 3-substituted isocoumarins — for example, achlisocoumarin I²⁾ and thunberginol A³⁾ — were isolated. Various methods are known for the synthesis of isocoumarin-containing structures.⁴⁾ Palladium-catalyzed intramolecular addition of a carboxylic acid to an alkene becomes an efficient route toward lactones.⁵⁾ Although this method has been applied to a synthesis of 3-substituted isocoumarins from *o*-alkenylbenzoic acids,⁶⁾ the catalytic use of palladium reagent and the use of more highly functionalized benzoic acid derivatives have not yet been described. We wish to report in this paper Pd-catalyzed cyclization of *o*-alkenylbenzoic acid derivatives and a further synthesis of isoquinolone from the isocoumarine obtained.

Treatment of 4,5-dimethoxy-2-styrylbenzoic acid (**1a**)^{7, 8)} with 1 eq of $PdCl_2(CH_3CN)_2$ in the presence of triethylamine provided 3-phenylisocoumarin **2a** and benzylidenephthalide **3a** in 80% yield (**2a** : **3a** = 96 : 4). In order to improve this reaction to a catalytic one, the $Pd(0)$ generated should be reverted back to $Pd(II)$ by the addition of an oxidant. The reactions were carried out with 5 mol% of palladium reagent and an oxidant such as $Cu(II)$ and O_2 at room temperature in THF for 12 h, giving **2a** and **3a**. However, neither the yield nor the cyclization selectivity were satisfied. Benzoquinone was found to be the best oxidant. The reaction with benzoquinone (1.1 eq) for 2 h

gave the isocoumarin **2a** in quantitative yield with high cyclization selectivity (Table I, entry 1).

The latter method was applied to cyclization of several *o*-alkenylbenzoic acids. The results are shown in Table I.⁹⁾ In the case of styryl compounds, the substituent on aromatic ring (R) affected cyclization selectivity. In the order of MeO > Me > CHO, the selectivity decreased according to electron-withdrawing ability (entry 2-4). On the other hand, *o*-hexenylbenzoic acid **1e** gave exclusively 3-butyliisocoumarin **2e** in good yield (entry 5).

Table I. $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ Catalyzed Cyclization of **1** in the Presence of Benzoquinone

Entry	1	R	Reaction time (h)	2 : 3	Yield (%)
1	1a	Ph	2	99 : 1	98
2	1b		2	93 : 7	90
3	1c		2	86 : 14	73
4	1d		2	74 : 26	82
5	1e	<i>n</i> -Bu	6	100 : 0	83

The reaction proceeded through acyloxypalladation followed by β -hydride elimination. Although the precise mechanism of 6-*endo* and 5-*exo* selectivity has not been clarified, the selectivity would be affected by the electron demand of carbon-carbon double bond.¹⁰⁾

The isocoumarins obtained were easily converted to the corresponding isoquinolones by treatment with primary amines. For example, treatment of **2a** with ammonia or methylamine in EtOH gave the isoquinolone **4** or **5**. This process will be very useful because direct cyclization of *o*-alkynylbenzamide **6** in basic medium gave only the benzylidenephthalimide **7**.¹¹⁾

Thus, we have identified a successful palladium-catalyzed cyclization method for the synthesis of isocoumarins.¹²⁾ The present method is easy to carry under mild conditions. This process is also applicable to the synthesis of isoquinolones, synthetic intermediates for benzo[c]phenanthridine alkaloids.¹³⁾

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- 7) The compounds **1a-1d** were prepared from methyl 2-iodo-4,5-dimethoxybenzoate and styrene derivatives by Heck reaction($\text{Pd}(\text{OAc})_2$, $(n\text{-Bu})_4\text{NCl}$, DMF, 100°C / 12 h), followed by hydrolysis.
- 8) We chose 4,5-dimethoxy derivatives **1** because our final synthetic targets are benzo[c]-phenanthridine alkaloids,¹³⁾ most of which possess the same oxygenation pattern on one aromatic ring as **1**.
- 9) All new compounds were satisfied by elemental analysis and spectral data.
- 10) In order to clarify the mechanism, the reactions with various types of substituted 2-styrylbenzoic acids are in progress.
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